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Unravelling the effect of adiposity on health: the epidemiology paradoxes

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In the current issue of *Obesity*, *Hulsegge et al* produce evidence from Dutch data that a rising BMI in populations during a 15-year follow up is strongly linked to increases in oxidative stress and inflammation markers compared to a stable BMI. Although that is true within the same generation, i.e. people born in the same year, the greater BMI across generations at the same age, was not associated with greater oxidative stress or inflammation.

In 2013, *Flegal et al* generated major academic and media excitement from a cross sectional analysis of BMI status by concluding that 'overweight' (qua BMI 25-30kg/m²) might be protective against all-cause mortality, making a case for an 'obesity paradox' (1). A commentary in *Obesity* argued that this may just be an issue of selection bias, among other potential explanations (2). But the study of *Hulsegge et al*, alongside other evidence, may suggest more complex interactions between overweight/obesity, or the measures used in epidemiology, and ageing. The use of BMI (alone) may also be misleading. In an analysis of UK data we showed that BMI and Waist Circumference (WC), both used as proxies for adiposity but both relatively weak correlates of body fat (they both explain less than 75% of the variance in body fat), showed progressively less agreement with increasing age. The proportion of individuals with elevated WC, but normal BMI, increased markedly with age (3). These conclusions were confirmed by similar analysis Australian data(4). If the relationships between BMI and body fat and muscle mass change with age, that may also occur between generations.

Epidemiology on CVD risk has mainly relied on the conventional risk-markers, Blood Pressure (BP), lipids, glycaemia. These do not characterise the entire pathological pathway, elevated oxidative and inflammatory markers may identify later pathological stages. All are related to adiposity, but not necessarily equally. Just as the diagnosis of type 2 diabetes, an 'obesity-related disease' does not require BMI >30, *Hulsegge et al* found an adverse relationship between rising BMI and oxidative stress/inflammation among participants whose BMI never exceeded 25kg/m² during the 15 year study-period.

It is likely that relationships between BMI, body fat, muscle mass and markers of disease development change with age, and possibly between generations. It is also possible that there are changes in the relationships with mortality of disease markers, such as BP, lipids, glycaemia or oxidative and inflammatory markers. Cross-sectional data on BMI alone are unlikely to give a detailed picture of adiposity and changes in body composition changes across the life-course. Longitudinal changes in body composition are always likely to be more sensitive markers of morbidity and mortality. 'Overweight' populations might experience lower mortality if they maintain a stable (but elevated) BMI over the years. They may also benefit by maintaining greater muscle mass, which would be invisible to BMI. More detailed measurements including WC and hip circumference cost little and might allow better estimation of changes in body composition(5). These, plus more complete characterisation of CVD risk markers might explain the 'obesity paradox'.

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